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EXAMINER	
BRISTOL, LYNN ANNE	
ART UNIT	**PAPER NUMBER**
1643	

NOTIFICATION DATE	DELIVERY MODE
06/21/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/535,433	FRIGERIO ET AL.	
	Examiner	Art Unit	
	Lynn Bristol	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 4/2/07.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1 and 34-86 is/are pending in the application.

4a) Of the above claim(s) 45,47,49,51 and 53-81 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1, 34-44, 46, 48, 50, 52 and 82-86 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date 5/18/05.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1 and 34-86 are all the pending claims for this application.

2. Claims 36, 40, 55, 56, 62 and 63 have been amended to recite sequence identifiers and new claims 82-86 have been added in the Reply of 4/2/07.

3. Applicants preliminary amendment of 2/2/06 to the specification to introduce sequence identifiers for peptides and primers, and on p. 6 of the preliminary amendment to introduce the "2.3-fold" higher recovery for $P(A)_5CY$ have been considered and entered.

Election/Restrictions

4. Applicant's election with traverse of Group I (Claims 1, 34-44, 46, 48, 50 and 52 (and new Claims 82-86)) in the reply filed on 4/2/07 is acknowledged. The traversal on pp. 13-14 of the Reply is on the ground(s) that the references (Frigerio et al., Vitale and Raikel, and Kiode et al.) cited in the Office Action of 2/2/07 are distinguishable from the instant claims and therefore the claimed special technical feature is a contribution over the art. Applicants allege that Frigerio does not disclose a modified Cα3 domain in the terminal 18 amino acid portion of the C-terminus for antibodies, and neither Vitale and Raikel or Koide disclose vacuolar sorting signals in antibodies, only plant proteins, which are non-analogous art.

This is not found persuasive for reasons of record and for the reasons set forth *infra*. Briefly, Frigerio fully appreciates that plant secretory pathways are particular in that protein diversion from secretion to vacuolar compartmentalization is known to occur

for some protein sequences, and even anticipates that "plant cells may deliver to the vacuole a proportion of recombinant mammalian proteins that are expected to be secreted" (p. 1484, Col. 1, ¶2). Frigerio specifically compares IgG and IgA/IgG hybrid in the plant expression system observing that the IgA Cα domains specifically contribute to this diversion for the hybrid antibody to plant vacuole compared to native IgG Fc domains. On p. 1489, Col. 2, ¶2 Frigerio teaches that sorting signals are required for soluble protein delivery to vacuoles and deletion of these sequences reroutes proteins towards secretion. Thus, contrary to Applicants allegation, Frigerio does not perform the experiments in a context void of any understanding or appreciation for specious vacuolar localization of recombinant proteins and the role of cryptic targeting sequences in plants. Vitale and Raikel, and Kiode et al. are cited for showing that even when heterologous plant proteins are expressed in transgenic plants, the role of cryptic signaling sequences is found to contribute to their vacuolarization. Thus extending this concept of signaling sequences to human recombinant proteins intended for secretion in transgenic plants is clearly contemplated by Frigerio. Vitale and Raikel, and Kiode et al. are cited for disclosing what some of those sequences may be.

Finally and contrary to Applicants assertion, nowhere in instant Claim 1 is the method limited to the modification occurring within the Cα3 or mu domain of the heavy chain. Claim 1 only requires that the antibody molecule comprise the Cα3 or mu domain. So even assuming *arguendo* Frigerio teaches modification in a Cα2 domain, the reference still reads on the claim.

The requirement is still deemed proper and is therefore made FINAL.

5. Claims 45, 47, 49, 51 and 53-81 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions of Groups 2-14, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 4/2/07.

6. Applicants election of species for the synthetic sequence (of general formula – $(Xaa_1)_mC(Xaa_2)_n$-) to be $(ala)_5cys(gly)_1$ is acknowledged.

7. Claims 1, 34-44, 46, 48, 50, 52 and 82-86 are all the pending claims under examination.

Information Disclosure Statement

8. The U.S. and international patent references and the non-patent literature references cited in the IDS of 5/18/05 have been considered and entered.

Specification

9. a) The specification is objected to because it does not provide sequence identifiers for the following sequences pursuant to 37 CFR 1.821 (c) and/or (d):

1) $X_1X_2X_3VSX_4$, p. 8, lines 7 and 31; p. 10, line 31, p. 11, lines 11 and 24;

b) The specification is objected to for omitting to include the name of the reference article described on p. 3, ¶¶ 1-4. Applicants refer to "the Frigerio paper" but it is not clear which of the Frigerio papers is incorporated by reference. Eighty one (81) Frigerio references published prior to the foreign priority filing date are returned by

Medline query. Applicants are advised to amend the specification to include the referenced journal article and without the introduction of new matter.

c) The underlined text occurring at: p. 11, line 33; p. 12, lines 1, 2 and 4; p. 15, line 18; p. 24, lines 29-31; and p. 25, line 5, is confusing as to whether the text was added to the application upon entry to national stage or whether this is for emphasis. Applicants are required to explain the meaning and origin of the underlined text.

Claim Objections

10. Claim 35 is objected to for an apparent typographical error: the article "the" should appear before "nucleotide sequence".

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 1, 34-44, 46, 48, 50, 52 and 82-86 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a) Claims 1, 34-44, 46, 48, 50, 52 and 82-86 recite the limitation "the completed heavy chain" in element (b) of Claim 1. There is insufficient antecedent basis for this limitation in the claim. Claim 1 recites the immunoglobulin heavy chain.

b) Claims 1, 34-44, 46, 48, 50, 52 and 82-86 are indefinite for the entire recitation in element (b) of Claim 1, because the recitation describes the modification of the

nucleotide sequence as causing the vacuolar targeting sequence to form a modified nucleotide sequence, when instead, the modification would seemingly occur in the region of a vacuolar targeting sequence in order to effect its function to target the protein to a vacuole.

c) Claims 1, 34-44, 46, 48, 50, 52 and 82-86 recite the limitation "the modified antibody heavy chain" in element (d) of Claim 1. There is insufficient antecedent basis for this limitation in the claim. Claim 1 recites an antibody molecule and an immunoglobulin heavy chain.

d) Claim 34 recites the limitation "the heavy chain molecule". There is insufficient antecedent basis for this limitation in the claim. Claim 1 recites an antibody molecule and an immunoglobulin heavy chain.

e) Claim 35 is indefinite for the entire "wherein" clause because it is not clear if the point mutations of the nucleotide sequence are intended to comprise the "deleting", "adding" and "replacing" limitations that follow in the claim or whether a point mutation is inclusive of the group of modifications. If the point mutation is inclusive of the group, Applicants are requested to provide an explanation of how the point mutations would differ from any of the following modifications as claimed.

f) Claim 35 is indefinite for the recitation "and/or" because it is not clear if the final limitation of the wherein clause is required or not.

g) Claims 38 and 39 recite the limitation "the heavy chain". There is insufficient antecedent basis for this limitation in either of the claims or in Claim 1. Claim 1 recites an immunoglobulin heavy chain.

h) Claim 39 recites improper Markush group language for "selected from" and should recite "selected from the group consisting of".

i) Claims 40, 42 and 44 recite the limitation "the nucleotide sequence modified". There is insufficient antecedent basis for this limitation in the claims or in Claim 1. Claim 1, element (b) recites a modified nucleotide sequence.

j) Claim 43 recites several limitations: "the modified amino acid" and "the completed heavy chain". There is insufficient antecedent basis for these limitations in the claim or in Claims 42 and 1.

k) Claim 43 is indefinite for the recitation "the modified amino acid is one or both of an isoleucine 3 amino acids and/or 10 amino acids from the C-terminus end of the completed heavy chain". It is not clear if the amino acid is required to have both positions modified because of the "and/or" language.

l) A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131

USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 44 recites the broad recitation, for example, "X_1= N, H or L", and the claim also recites "preferably N" which is the narrower statement of the range/limitation. The are seven (7) other iterations of this sort in Claim 44.

m) Claims 52 and 86 recite the limitation "the antibody". There is insufficient antecedent basis for this limitation in the claims or in Claim 1. Claim 1 recites antibody molecule.

n) Claims 52 and 86 are indefinite for the recitation "the antibody is subjected to protease digest to for Fab or F(ab')$_2$ fragments" because there is no art recognized meaning for a Fab or F(ab')$_2$ fragments protease digest. If the antibody is intended to be protease digested to *produce* Fab or F(ab')$_2$ fragments then the claims should be written as such.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description Requirement

12. Claims 1, 34-38, 40-44, 46, 48, 50, 52 and 82-86 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter, which was not described in the specification in such

a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The claims encompass any modified C-terminal heavy chain comprising a α3 or mu domain where the vacuolar targeting signal sequence is diminished in functional capacity. The claims broadly encompass general formulas comprising the original sequence and the modified sequence for the α3 or mu domains, yet the only modified or synthetic sequences taught in the entire specification are those in Claim 39 for SEQ ID NOS: 7, 8, 9 and 69. Therefore, the claims encompass a genus of synthetic or modified C-terminal peptides defined solely by a principal biological property, which is simply a wish to know the identity of any material with that biological property. Accordingly, there is insufficient written description encompassing a "synthetic nucleotide sequence" because the relevant identifying characteristics of the genus such as structure or other physical and/or chemical characteristics of a "synthetic nucleotide sequence" which encodes a C-terminus 18 amino acids of the heavy chain to remove or reduce the vacuolar targeting signal sequences are not set forth in the specification as-filed, commensurate in scope with the claimed invention. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (see page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (see Vas-Cath at page 1116).

Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddles v.Baird, 30 USPQ2d 1481, 1483. In Fiddles v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence. Thus, the specification fails to describe these DNA sequences. The Court further elaborated that generic statements are not adequate written description of the genus because it does not distinguish the claimed genus from others, except by function.

In the absence of structural characteristics that are shared by members of the genus of a "synthetic nucleotide sequence" useful for reducing or removing the vacuolar targeting signaling sequence from the α3 or mu domains of the heavy chain for the antibody molecule; one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. See University of California v. Eli Lilly and Co. 119 F.3d 1559; 43 USPQ2d 1398 (Fed. Cir. 1997).

Scope of Enablement Requirement

13. Claims 1, 34-38, 40-44, 46, 48, 50, 52 and 82-86 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making and expressing an antibody comprising a modified heavy chain comprising synthetic C-terminal regions for the α3 domain comprising SEQ ID NOS: 7, 8, 9 *or* 69 and comprising a light chain, where the vacuolarization of the heavy chain is reduced or removed when the protein is expressed in transgenic plant cells, and the antibody molecule has specific binding ability for a given antigen in having both a heavy and light chain, Fab, or two sets thereof for $F(ab')_2$, does not reasonably provide enablement for expressing a functional antibody having only a heavy chain much less any heavy chain with a modified α3 or mu domain, or any transgenic plant- or plant cell-expressed antibody having reduced or removed vacuolar targeting by introduction of just any synthetic nucleotide sequence or synthetic tail into the α3 or mu domain of the heavy chain or any α3 or mu domain-modified heavy chain expressed by the host and having retained specific binding affinity in the absence of a light chain. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability of the art, the breadth of the claims,

the quantity of experimentation which would be required in order to practice the invention as claimed.

Nature of the Invention/ Skill in the Art

The claims are broadly drawn to a method of making any antibody molecule containing an Ig heavy chain comprising α3 or mu domain where the nucleotide sequence encoding the heavy chain is modified in the C-terminal 18 amino acid residues in order to reduce or remove the vacuolar targeting signal sequences and where the modified nucleotide sequence is expressed in a host cell to form a modified antibody heavy chain for secretion form the host cell. The claims are broadly drawn to the modifications that can be introduced into a general C-terminal sequence for the heavy chain

Disclosure in the Specification

The specification discloses as examples of the modified heavy chain peptides having the diminished localization to plant cell vacuoles (or increased secretion) when the C-terminal peptide is of SEQ ID NO: 7, 8, 9 or 69. The specification makes a general disclosure for the generic formulas that the C-terminal domains may comprise and which allegedly confer the improved secretory property for the antibody in plant cell expression systems, but the no other working examples of antibodies having modified heavy chains are disclosed. Notably, in order for the antibody molecule to be filly binding, it must also be associated with a light chain.

Thus, one of skill in the art is left to determine which of the infinite number of modification(s) to the region of any human Ig antibody can be made to create a

modified heavy chain having a loss-in vacuole localizing function or improved secretion over the native counterpart, where the modified antibody heavy chain still retains antigen specificity. Without such guidance, the changes which can be made in the Ig's heavy chain structure and still maintain biological activity is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue. See Amgen, Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F,2d 1200, 18 USPQ 1016 (Fed. Cir. 1991) at 18 USPQ 1026 1027 and Ex parte Forman, 230 USPQ 546 (BPAI 1986).

Prior art teachings/Unpredictability/Undue Experimentation

A) Modification to Antibody Structure Can Effect Overall Biological Properties

Protein chemistry is probably one of the most unpredictable areas of biotechnology. Ibragimova and Wade (Biophysical Journal, Oct 1999, Vol. 77, pp. 2191-2198) teach that factors affecting protein folding and stability are governed by many small and often opposing effects and that even when the "rules" are know for altering the stability of a protein fold by the introduction of a single point mutation the result is not reliable because the balance of forces governing folding differs for different protein sequences, and that the determination of the relative magnitude of the forces governing the folding and stability of a given protein sequence is not straightforward (page 2191, first column, lines 12-17 and second column, lines 3-8).

For example, the replacement of a single lysine at position 118 of the acidic fibroblast growth factor by a glutamic acid led to a substantial loss of heparin binding, receptor binding, and biological activity of the protein (see Burgess et al, Journal of Cell

Biology Vol 111 November 1990 2129-2138). In transforming growth factor alpha, replacement of aspartic acid at position 47 with asparagine, did not affect biological activity while the replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen (see Lazar et al Molecular and Cellular Biology Mar 1988 Vol 8 No 3 1247-1252). Replacement of the histidine at position 10 of the B-chain of human insulin with aspartic acid converts the molecule into a superagonist with 5 times the activity of nature human insulin. Schwartz et al, Proc Natl Acad Sci USA Vol 84:6408-6411 (1987). Removal of the amino terminal histidine of glucagon substantially decreases the ability of the molecule to bind to its receptor and activate adenylate cyclase. Lin et al Biochemistry USA Vol 14:1559-1563 (1975).

These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification, will often dramatically affect the biological activity of a protein. These references further demonstrate and suggest the general need for further investigation into this form of engineered antibody. Therefore, due to the unpredictability of constructing any human antibody with a modified Fc domain in general, and more specifically, with respect to the amount of experimentation required to select and target amino acid residues in the Fc domain, produce and screen Igs comprising modified Fc domains conferring a loss-in vacuole localizing function (or gain in secretion) more especially in transgenic plant expression, and in view of the insufficient guidance and/or working examples concerning the making and using of any Fc modified human Ig with respect to its antigen targeting specificity, effector function, etc., one skilled in the art would not know how to practice the broadly

claimed invention, i.e., making and using a functional Fc modified human Ig heavy chain comprising a modified α3 or mu domain without undue experimentation.

B) An Antibody Molecule Containing Anything Less than a Full Complement of VH and VL CDRs May be Compromised in Binding Affinity

The claims (especially Claim 1) encompass an antibody molecule defined only by the expression of a modified heavy chain from a host cell. Claims 52 and 86 are the only claims defining the presence of a light chain where the antibody molecule is either a Fab or $F(ab')_2$ fragment.

It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 1982 Vol 79 page 1979). Rudikoff et al.

teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function.

Therefore, in view of the lack of guidance, lack of examples, and lack of predictability associated with regard to producing and using the myriad of antibody molecules encompassed in the scope of the claims, one skilled in the art would be forced into undue experimentation in order to practice the broadly claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

14. Claims 1, 34, 35, 38, 40, 41, 46, 48 and 50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Frigerio et al. (Plant Physiology 123:1483-1493 (August 2000); cited in the IDS of May 18, 2005 and the PTO 892 form of 2/2/07) in view of Vitale and Raikhel (Trends in Plant Science 4(4):149-155 (April 1999); cited in the IDS

of May 18, 2005 and the PTO 892 form of 2/2/07), Koide et al. (Plant Cell Physiol. 40(11):1152-1159 (1999); cited in the IDS of and the PTO 892 form of 2/2/07) and Matsuoka et al. (J. Exp. Bot. 50:165-174 (1999); cited in the IDS of 5/18/05).

The interpretation of the claims is discussed supra.

The claimed method was prima facie obvious at the time of the invention over Frigerio, Vitale and Raikhel, Kiode and Matsuoka.

Frigerio discloses that the α-domains in the hybrid IgA/G heavy chains might be involved in intracellular retention and vacuolar delivery in plant cells. Frigerio speculated several causes for this observation, e.g., stress on the ER by the recombinant protein, structural defects in the in the α-domains, cysteine residues in the C-terminus of heavy chains of IgA and secretory IgM, and the extra Cα2 domains might affect interactions with chaperones and quality control mechanisms by ER. As specifically addressed supra, Frigerio explicitly discussed the evidence from other recombinant expression systems recognizing the existence of cryptic sequence residues that mediated heterologous proteins in vacuole trafficking. Thus Frigerio fully contemplated the existence of such sequences in mediating these events with the possible application to the hybrid IgA/G antibodies under study in order to mask vacuolar sorting of the recombinant antibodies. Frigerio did not explicitly disclose which of the sequences in the Cα3 or mu domain (e.g., C-terminal VS or SV repeats) might contribute to this observation. Vitale and Raikhel, Kiode and Matsuoka rectify this deficiency in their disclosures.

Vitale and Raikhel disclose the criticality of the VS or SV sequence present in the C-terminal of heterlogous proteins expressed in transgenic plant cells and specifically involved in vacuole targeting.

Koide disclose the criticality of the VS or SV sequence present in the C-terminus of the potato protein in vacuole targeting.

Matsuoka disclose specifically disclose that the function of C-terminal vacuolar sorting signals can be decreased or even abolished by adding two to four glycine residues downstream of the sorting signal.

One skilled in the art would have been motivated at the time of the invention to have created the method for producing an antibody molecule comprising in its heavy chain a modified Cα3 or mu domain such that the heavy chain would be diverted from vacuole targeting in the plant host cell and secreted, and the skilled artisan would have been assured of reasonable success based on the combined disclosures of Frigerio, Vitale and Raikhel, Kiode and Matsuoka. Frigerio discloses that vacuolar delivery of sIgA (C-alpha 2 and C alpha 3)/G in plants is mediated by the alpha domains present in the hybrid alpha/gamma-heavy chains and indicates that plant secretory system recognizes cryptic vacuolar signaling domain that delivers the hybrid molecule to the vacuole rather than being secreted. Frigerio discusses several vacuolar signaling domains recognized in other plant proteins and which may bear homology to the alpha domain. Vitale and Raikhel disclose peptides involved in the sorting of soluble vacuolar proteins which comprise VS or SV repeats and are found, for example, in C-terminal propeptides of plants. Koide discloses the VS and SV repeats are found in many plant

peptides. Matsuoka appreciates that modifications in or around the vacuolar sorting signal can reduce the recombinant protein trafficking to the vacuole and instead result in improved secretion in the host plant cell. Because of the advantages of producing recombinant antibodies in host plant cells as appreciated by Frigerio and the problems associated with inherent VS and SV repeat residues in expressed recombinant proteins that were present in the antibodies of Frigerio, that decreased the amount of secreted heavy chain protein, one skilled in the art would have found sufficient motivation to look to the references of Vitale and Raikhel, Kiode and Matsuoka where the signaling sequences for plant expressed and recombinant expressed proteins in host plant cells were identified as causing or contributing to vacuole targeting and modifying the antibodies of Frigerio to diminish or eliminate the VS or SV repeats found in the heavy chain C-terminus of the Cα3 or mu domain in order to improve the overall secretion of the heavy chain. Because there was more than sufficient motiivation and the cumulative evidence pointed to such cryptic residues, one skilled in the art could have reasonably generated modified heavy chains based on the cumulative information about protein secretion in plants to obtain the instant claimed method for generating such antibody molecules. For all of these reasons, the claims were prima facie obvious at the time of the invention.

Conclusion

15. No claims are allowed.

LARRY R. HELMS, PhD
SUPERVISORY PATENT EXAMINER

16. The heavy chain C-terminus peptides of Claim 39 appear to be free of art. A search of commercial protein sequence databases against each of peptide sequences for SEQ ID NO: 7, 8, 9 and 69 did not identify any other peptides having 100% identity or homology with instant claimed peptides.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynn Bristol whose telephone number is 571-272-6883. The examiner can normally be reached on 8:00-4:00, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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